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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/751,299	12/28/2000	Mark Madden	DIVER1440-2	8629

25225 7590 05/15/2006

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EXAMINER
KAM, CHIH MIN

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 05/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/751,299	MADDEN ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,32,36,37,44,49,50 and 52-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *31,32 and 49* is/are allowed.

6)☒ Claim(s) *36, 37, 44, 50 and 52-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Request for Continued Examination (RCE) filed on March 3, 2006 under 37 CFR 1.114 is acknowledged. An action on the RCE follows.

Status of the Claims

2. Claims 31, 32, 36, 37, 44, 49, 50 and 52-80 are pending.

Applicants' amendment filed March 3, 2006 is acknowledged. Applicants' response has been fully considered. Claims 31, 32, 36, 37, 44, 49, 50, 53 and 62 have been amended, claims 45-48 and 51 have been cancelled, and new claims 66-80 have been added. Therefore, claims 31, 32, 36, 37, 44, 49, 50 and 52-80 are examined.

Withdrawn Claim Objections

3. The previous objection to claims 51, 53 and 62-65 is withdrawn in view of applicant's cancellation of the claims, and applicant's amendment to the claim in the amendment filed March 3, 2006.

Withdrawn Claim Rejections – 35 USC § 112

4. The previous rejection of claims 31, 32, 36, 37, 49, 52 and 54-61 under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicant's amendment to the claims and applicant's response at page 17 in the amendment filed March 3, 2006.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 44, 50 and 66-80 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of stereoselectively producing an alpha-substituted carboxylic acid having the structure of $C(R_1)(R_2)(E)(COOH)$, where R_1, R_2 and E is defined in the claim 44, using a polypeptide of nitrilase, wherein the nitrilase consists of SEQ ID NO:2 or SEQ ID NO:4, or, is encoded by a nucleic acid consisting of SEQ ID NO:1 or SEQ ID NO:3, does not reasonably provide enablement for a method of stereoselectively producing an alpha-substituted carboxylic acid having the structure of $C(R_1)(R_2)(E)(COOH)$, where R_1, R_2 and E is defined in the claim 44, using a polypeptide of nitrilase, wherein the nitrilase has an amino acid sequence having at least 80% sequence identity to the sequence of SEQ ID NO:2 or SEQ ID NO:4 and retains the biological activity of SEQ ID NO:2 or SEQ ID NO:4, or, is encoded by a nucleic acid having at least 80% sequence identity to the sequence of SEQ ID NO:1 or SEQ ID NO:3 and retains the same enzyme activity as the enzyme encoded by the sequence of SEQ ID NO:1 or SEQ ID NO:3, or, is encoded by a nucleic acid that hybridizes under stringent conditions to a sequence of SEQ ID NO:1 or SEQ ID NO:3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 44, 50 and 66-80 encompass a method of stereoselectively producing an alpha-substituted carboxylic acid using a polypeptide of nitrilase, wherein the nitrilase has an amino acid sequence having at least 80% sequence identity to the sequence of SEQ ID NO:2 or SEQ ID NO:4 and retains the biological activity of SEQ ID NO:2 or SEQ ID NO:4, or, is encoded by a nucleic acid having at least 80% sequence identity to the sequence of SEQ ID NO:1 or SEQ ID NO:3 and retains the same enzyme activity as the enzyme encoded by the sequence of SEQ ID

NO:1 or SEQ ID NO:3, or, is encoded by a nucleic acid that hybridizes under stringent conditions to a sequence of SEQ ID NO: 1 or SEQ ID NO:3. The specification, however, only discloses cursory conclusions without data supporting the findings, which state that the present invention provides methods for producing enantiomerically pure α-substituted carboxylic acids, such as α-amino acids and α-hydroxy acids, the methods including combining an aldehyde or ketone with a cyanide and an ammonia-containing compound or an ammonium salt, in the presence of a nitrilase which stereoselectively hydrolyzes the amino nitrile or cyanohydrin intermediate, under conditions sufficient to produce the carboxylic acid, wherein the nitrilase has an amino acid sequence of SEQ ID NO:2 or SEQ ID NO:4 or sequences having at least 70% identity thereto and having nitrilase activity (pages 2-3). There are no indicia that the present application enables the full scope in view of the claimed method using a nitrilase related to SEQ ID NO:2 or SEQ ID NO:4 as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the absence or presence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the functional amino acid sequences having at least 80% sequence identity to the sequence of SEQ

ID NO:2 or SEQ ID NO:4, being encoded by a nucleic acid having at least 80% sequence identity to the sequence of SEQ ID NO:1 or SEQ ID NO:3, or, being encoded by a nucleic acid that hybridizes under stringent conditions to a sequence of SEQ ID NO:1 or SEQ ID NO:3, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

Example 1 shows using the nitrilase of SEQ ID NO:2 or SEQ ID NO:4 to stereoselectively produce (S)-phenylglycine from phenylglycineonitrile (or benzaldehyde, KCN and NH_4Cl). However, there are no examples indicating the use of amino acid sequences related to SEQ ID NO:2 or 4, amino acid sequences encoded by nucleotide sequences having at least 80% sequence identity to the sequence of SEQ ID NO:1 or SEQ ID NO:3, or, amino acid sequences encoded by nucleotide sequences that hybridizes under stringent condition to the sequence of SEQ ID NO:1 or SEQ ID NO:3 as nitrilase in the claimed methods.

(3). The state of the prior art and relative skill of those in the art:

The related art (e.g., the references shown as Exhibits B-D in the amendment filed October 31, 2005) teach the sequences of several nitrilase, however, these sequences are not the same as the sequence of SEQ ID NO:2 or 4. Furthermore, there is no description regarding the sequences for variants of nitrilase peptides. Since the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide teachings on the identification of the sequences of various nitrilase peptides that are active in stereoselectively producing an alpha-substituted carboxylic acid.

(4). Predictability or unpredictability of the art:

The claims are directed to a method of stereoselectively producing an alpha-substituted carboxylic acid using a polypeptide of nitrilase, wherein the nitrilase has an amino acid sequence having at least 80% sequence identity to the sequence of SEQ ID NO:2 or SEQ ID NO:4, is encoded by a nucleic acid having at least 80% sequence identity to the sequence of SEQ ID NO:1 or SEQ ID NO:3, or, is encoded by a nucleic acid that hybridizes under stringent conditions to a sequence of SEQ ID NO: 1 or SEQ ID NO:3. While the specification indicates the polypeptide or nucleic acid sequences of nitrilase having sequence identities at least about 80% to SEQ ID NO: 2 or 4, or SEQ ID NO: 1 or 3, respectively (page 11, lines 20-30; page 42, lines 5-23); or amino acid sequences of nitrilase being encoded by a nucleic acid that hybridizes under stringent conditions to a sequence of SEQ ID NO: 1 or SEQ ID NO:3 (page 39, lines 8-19; page 40, line 5-page 42, line 4), it does not identify any of the peptide variants, nor indicates the structure and function relationship for the variants. Thus, the amino sequence of a functional nitrilase peptide is unpredictable.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of stereoselectively producing an alpha-substituted carboxylic acid using a polypeptide of nitrilase related to SEQ ID NO:2 or 4. While the specification indicates using the nitrilase of SEQ ID NO:2 or SEQ ID NO:4 to stereoselectively produce (S)-phenylglycine from phenylglycineonitrile (or benzaldehyde, KCN and NH_4Cl; Example 1), the specification does not describe the use of amino acid sequences related to SEQ ID NO:2 or 4 (e.g., sequences having at least 80% sequence identity to the sequence of SEQ ID NO:2 or 4), the amino acid sequences encoded by nucleotide sequences having at least 80%

sequence identity to the sequence of SEQ ID NO:1 or SEQ ID NO:3, or, the amino acid sequences encoded by nucleotide sequences that hybridizes under stringent condition to the sequence of SEQ ID NO:1 or SEQ ID NO:3 as nitrilase in the claimed methods. Moreover, there are no working examples indicating the claimed methods associated with variants. Since the specification does not provide sufficient teachings on the make/use of the peptide variants of nitrilase in the claimed methods, it is necessary to have additional guidance and to carry out undue experimentation to identify active nitrilase polypeptides in the claimed methods and to assess the effects of these nitrilase polypeptide.

(6). Nature of the Invention

The scope of the claims encompasses a method of stereoselectively producing an alpha-substituted carboxylic acid using a polypeptide of nitrilase related to SEQ ID NO:2 or 4, but the specification does not demonstrate the make/use of various nitrilase peptide variants in the claimed method. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working examples do not demonstrate the claimed methods associated with variants, the sequences of active nitrilase peotides are unpredictable, and the teaching in the specification is limited, therefore, it is necessary to have additional guidance and to carry out undue experimentation to make/use the active nitrilase peotides in the claimed methods.

Response to Arguments

Applicants indicate that the specification enabled the skilled artisan at the time of the invention to make and use, and in particular, to identify or screen for, the claimed genus of nitrilases and nitrilase-encoding polynucleotides without undue experimentation and have

provided evidence and expert declaration to support this argument (see, e.g., Applicants' response of July 17, 2003, pages 30 to 32, including Dr. Jennifer Chaplin's expert declaration). Claims 44 and 50 as amended and new claims 67-80 encompass genera of nucleic acids progressively smaller in scope than the embodiments previously indicated in the claimed invention. Applicants also indicate the state of the art at the time of the invention and the level of skill of the person of ordinary skill in the art, e.g., screening enzymes, and nucleic acids encoding enzymes, for nitrilase activity such that the enzyme produces an alpha-substituted carboxylic acid, was very high. As analogous to In re Wands and as declared by Dr. Jennifer Ann Chaplin, using the teaching of the specification and other protocols known in the art at the time of the invention one skilled in the art could have successfully practiced the methods of the invention without undue experimentation, including identifying enzymes for used in the claimed methods without specific guidance as to which residues to change, or not change. Applicants have run a routine, simple sequence alignment comparison of known nitrilase sequences with exemplary sequences of the invention to identify regions of identity and dissimilarity between nitrilases as guidance as to which residue could, or could not, be modified (see Exhibit A). Accordingly, the specification and the art provided sufficient guidance to the skilled artisan to reasonably enable him or her how to make and use the genera of nitrilase sequences of the invention without undue experimentation (see pages 18-29 of the response).

Applicants' response and Declaration of Jennifer Ann Chaplin have been considered. However, the arguments are not fully persuasive because of the following reasons. The specification only describes the polyeptides of SEQ ID NOs: 2 and 4 as nitrilases and

their activity on phenylglycinonitrile (see Example 1). There is no description on the structure and function relationship in the nitrilase peptide variants of SEQ ID NOs: 2 and 4, and how their sequences reflect their nitrilase activity. Although several nitrilase sequences were known (see references Exhibits B-D) at the time of filing of the instant application, these sequences are different from the sequence of SEQ ID NO:2 or 4. Furthermore, the prior art is relatively silent on the generic structure of nitrilases. Thus, the ability to vary the sequences disclosed and maintain nitrilase activity, in particular stereoselective nitrilase activity, is unpredictable. While the instant specification describes means for assaying nitrilase activity or identifying other nitrilase genes encoding polypeptides similar to SEQ ID NOs: 2 and 4 using hybridization methods, these methods do not enable one of skill in the art to make all, or a relevant portion of, the polypeptides used in the methods within the scope of the claims because the ability to find other nitrilases, which are structurally related to SEQ ID NOs: 2 or 4, is not equivalent to the ability to make other nitrilases which are variants of SEQ ID NO:2 or 4 as required by the statute (i.e., to make and use") since no description in the specification or the art identifies particular residues whose encoding is important within the disclosed sequence so that its nitrilase-nature is maintained. Thus, one of skill in the art would be unable to predict the structure of the other members of the genus in order to make such members. Therefore, the instant claims are not enabled to the full extent of their scope (see also page 7 of the previous Office Action dated June 30, 2005).

6. Claims 66 and 72-74 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 66 and 72-76 are directed to a method for producing an alpha-substituted carboxylic acid using a polypeptide having nitrilase activity, wherein the alpha-substituted carboxylic acid having the structure of $C(R_1)(R_2)(E)(COOH)$, wherein E is $-N(R_x)_2$ or -OH, wherein each R_x is each independently -H or lower alkyl, substituted or unsubstituted alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclic, wherein said substituents are lower alkyl, hydroxy, alkoxy, mercapto, cycloalkyl, heterocyclic, aryl, heteroaryl, aryloxy, or halogen; or, wherein each R_x is each independently -H or lower alkyl, OH, substituted or unsubstituted alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclic. While the specification indicates E is $-N(R_x)_2$ or -OH, and each R_x is -H or lower alkyl (see page 3, line 23), the specification does not describe R_x is OH, substituted or unsubstituted alkyl, alkenyl, alkynyl, aryl, heteroaryl, or cycloalkyl, heterocyclic, wherein said substituents are lower alkyl, hydroxy, alkoxy, mercapto, cycloalkyl, heterocyclic, aryl, heteroaryl, aryloxy, or halogen. The lack of description of R_x being OH, substituted or unsubstituted alkyl, alkenyl, alkynyl, aryl, heteroaryl, or cycloalkyl, heterocyclic, and the substituents being lower alkyl, hydroxy, alkoxy, mercapto, cycloalkyl, heterocyclic, aryl, heteroaryl, aryloxy, or halogen in the claimed methods, and the lack of representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 36, 37, 44, 50, 52-65, 67-72 and 77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 36, 37 and 52-65 are indefinite because the claim recites a method for stereoselectively producing an alpha-amino acid by contacting an aldehyde or ketone with a cyanide-containing compound and ammonia to produce amino nitrile, however it also recites E being OH in the structure of $C(R_1)(R_2)(E)(COOH)$, which is not an alpha-amino acid. Claim 36 recites the limitation "said α-substituted carboxylic acid" in line 12. There is insufficient antecedent basis for this limitation in the claim. Claims 37 and 52-65 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

9. Claims 44, 50, 67-71 and 77 are indefinite because of the use of the term "the nucleic acid encodes an enzyme that retains the same enzymatic activity as the enzyme encoded by the nucleic acid sequence from which it varies". The term cited renders the claim indefinite, it is not clear what the first nucleic acid, the second nucleic acid, or "it" refers to, does it refer to a nucleic acid having at least 80% sequence identity or the nucleotide sequence of SEQ ID NO:1 or 3. Claims 67-71 and 77 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

10. Claim 72 recites the limitation "amine" in line 11. There is insufficient antecedent basis for this limitation in the claim since step (a) does not recites this limitation.

11. Claims 66 and 78-80 are indefinite as to what stringent condition is used for hybridization step because the claim only recites the condition for washing step, it is not clear what condition is used for hybridization. Claims 79-80 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

Conclusion

12. Claims 36, 37, 44, 50 and 52-80 are rejected; and claims 31, 32 and 49 are free of art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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PATENT EXAMINER

CMK
May 9, 2006